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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,071	07/23/2001	Mayumi Tomikawa	522.1921D2	2943
21171	7590	07/09/2007	EXAMINER	
STAAS & HALSEY LLP			BORIN, MICHAEL L	
SUITE 700			ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	09/910,071	TOMIKAWA ET AL.
	<b>Examiner</b>	<b>Art Unit</b>
	Michael Borin	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 20 April 2007.  
 2a) This action is FINAL.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 13-15 and 24-26 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 13-15, 24-26 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____. _____	6) <input type="checkbox"/> Other: _____

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/20/2007 has been entered.

#### ***Status of Claims***

1. Claims 13-15, 24-26 are pending. Claims 13,24 are amended.

Rejections not reiterated from previous Office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

#### ***Claim Rejections - 35 USC § 112, second paragraph.***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 13-15, 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The rejection is applied for the following reasons.

Claims 13,24: The term "elements" as related to now claimed "amino acid sequence of protein molecule" is not quite clear. What constitute an "element"? Specification, paragraph [0150} addresses "elements including an atom or an atomic group", but then it is not clear what else is being included in an "element" and whether any atom (e.g., hydrogen atom) is considered to be an "element".

#### **Claim Rejections - 35 USC § 101 (utility)**

3. Claims 13-15, 24-26 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The rejection is maintained for the reasons of record and further in view of the following:

The instant claims are amended to limit the scope of the claims to comparing three-dimensional structures of amino acid sequences of "probe" and "target" proteins and making a determination that if three-dimensional coordinates are somewhat similar, the sequences have similar functions. The claims do not recite any particular function or any other practical application of the method.

As stated in the rejection,

*even if the discussion of utility is to be limited to analyzing of 3D structures of polypeptides (rather than "sequences of atoms" or "atomic group"), such comparison is a result which lacks substantial utility as subsequent research is needed to identify the utility of*

*finding such 3D similarities. Thus, Zu-Kang (Folding and Design , 1, 123-132, 1996) teaches that studies based on superimposition of 3D structures are “bound to be misleading” (end of Abstract). Zu-Kang discusses that structure/structure alignments are often used in the analysis of conserved features of protein folds but conclusions deriving from such studies can be misleading, as structure alignments are ambiguous. (p. 129).*

*There is a prevailing tenet that protein structures are more conserved than sequences. This requires that such structurally conserved pairs can be identified in a unique fashion. When alternative alignments exist which are indistinguishable in geometric terms, this task becomes difficult or impossible unless additional criteria are available that allow us to discriminate the set of evolutionarily related residue pairs from those pairs that are only geometrically equivalent. Examples of such additional features that could be used to identify conserved residues are a significant number of residue identities in one alignment or a match of functional residues. However, most sets of alternative alignments found in this study are indistinguishable by these criteria and further investigation of this issue will be an interesting exercise. In any case, protein pairs that can be aligned in alternative ways are the rule rather than exceptions (Table 1) and unresolvable ambiguities in structural similarity support the argument in favour of convergent rather than divergent evolution.*

*(p. 128-129)*

*Thus, even if the claimed method provided determining degree of spatial similarity for polypeptides, identification of significance of the determined similarity with respect to a “function” would require further research. As such, the claimed method lacks substantial utility.*

Applicant has not provided any comments with respect to the above rejection.

Examiner maintains that, as Zu-Kang reference states, the task of assigning function from a structure similarity "becomes difficult or impossible unless additional criteria are available that allow us to discriminate the set of evolutionarily related residue pairs from those pairs that are only geometrically equivalent". Thus, even if the method as now claimed addresses determining degree of spatial similarity for polypeptides, identification of significance of the determined similarity with respect to a "function" would require further research. As such, the claimed method lacks substantial utility.

4. Claims 13-15, 24-26 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

**Claim Rejections - 35 USC § 101 (non-statutory)**

5. Claims 13-15, 24-26 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The rejection is applied for the reasons of record and further in view of the following.

The instant claims are amended to limit the scope of the claims to comparing three-dimensional structures of amino acid sequences of "probe" and "target" proteins and making a determination that if three-dimensional coordinates are somewhat similar, the sequences have similar functions.

The instant claims are drawn to a computer process whereby, based on similarity in 3-D structures of "sequences of amino acid residues" of proteins of a biological substance, a determination is made whether a function of the first "sequences of atoms" or "atomic group" is equivalent to a function of the second "sequences of atoms" or "atomic group".

To address the "non-statutory" rejection, the claims are amended to recite superposed display to a display unit.

Examiner agrees that such output provides a tangible result, and thus satisfies the "tangible" prong of the "useful, tangible and concrete" criteria for computational methods. However, in order to be directed to statutory subject matter, the invention as claimed must satisfy all three criteria of being useful, and concrete, and tangible. In the instant case, as discussed in the utility rejection above, the invention does not satisfy the criteria of utility requirement.

Further, If the specification discloses a practical application of a § 101 judicial exception, but the claim is broader than the disclosure such that it does not require a practical application, then the claim must be rejected. In the instant case, the claims are directed to comparing not the coordinates of the amino acid residues but to comparing three-dimensional coordinates of unspecified "elements", and thus, as addressed previously, encompasses determining "function" of e.g., such sequence of atoms as C-C-O-P, or C-C-C, or atomic group such as CH<sub>3</sub> (i.e., groups of atoms or atomic groups which are unlikely to have a meaningful "function"). Therefore, the claims are broader than the statutory embodiments of the claim which might have had a potential utility.

Taken together, the claims are directed to non-statutory subject matter as the claimed invention does not "transform" an article or physical object to a different state or thing, and the final result achieved by the claimed invention does not satisfy all three criteria of being useful, and concrete, and tangible.

***Claim Rejections - 35 USC 102.***

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --  
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 13-15, 24-26 are rejected under 35 U.S.C. 102(b) as anticipated by Flaherty et al. or Mosimann et al.

Flaherty et al. describes comparison of muscle actin and heat shock cognate protein and demonstrate that calculating of rmsd between comparable spatial fragments shows close similarity of the structure of these proteins. See abstract. The reference concludes that the spatial similarity between actin and heat shock cognate protein suggest that there may be similarities in their functions. P. 5044-5045.

Mosimann et al. describe comparison of molecular models of P-30 protein and pancreatic RNase. The all atom superposition of active site residues of the P-30 and an identically minimized RNase structure has a root square deviation of 0.52A. Spatial similarity in the structures suggest similar pyrimidine specificity, i.e., similar function.

Art Unit: 1631

See abstract. With respect to the use of rmsd , the referenced method uses it both to confirm alignment and to use it as a predetermined threshold, – see p. 395, first paragraph, for example, describing that distance of 2.6. A was set as arbitrary threshold to consider spatial similarity.

As the instant claims are drawn to method of analyzing three-dimensional structures by generating correspondence between set points describing two three-dimensional structures and calculating root mean square distance (rmsd) between the corresponding elements, the claims read on any reference teaching comparison of two three dimensional protein structures and calculating rmsd therefor. The references used in the rejection are exemplary of this commonly used approach to comparing 3-D structures.

With respect to Flaherty reference, applicant seems to argue that the instant method is distinguishable from Flaherty because the method steps in the reference "are not based on calculations" or "is different from calculation operations utilized in the present claimed invention". First, the referenced method is based on steps which are computational, i.e., based on calculations same as the claimed method. Second, it is not clear what particular "calculation operations utilized in the present claimed" that distinguish the instant method are meant by applicant. Third, even if there were any steps designed to automate adjustment or superimposition steps, "merely using a

computer to automate a known process does not by itself impart nonobviousness to the invention". MPEP, chapter 2106 VI.

With respect to Mosimann method, applicant argues that the method requires a two-step procedure. The instant method is claimed using "comprising" language which is open to any steps other than immediately recited.

In addition, applicant previously argued that Mosimann et al reference, as now argued about Flaherty reference, uses manual alignment using inspection by eye, compared to analyzing by computer processor in the instant method. Fig. 1 of Morrisman.

Examiner maintains that as the instant claims are drawn to method of analyzing three-dimensional structures by generating correspondence between set points describing two three-dimensional structures and calculating root mean square distance (rmsd) between the corresponding elements, the claims read on any reference teaching comparison of two three dimensional structures and calculating rmsd therefor. The references used in the rejection are exemplary of this commonly used approach to comparing of 3-D structures.

The rejection is maintained.

7. Claims 13-15, 24-26 are rejected under 35 U.S.C. 102(b) as anticipated by Lackner et al (Protein Engineering, Vol. 13, No. 11, 745-752, 2000).

Lackner et al. describe method of finding 3D similarities between protein structures using ProSup algorithm which determines segments that can fit under RMSD cutoff.

The method compares structure of fragments of two proteins by first, selecting set points in the fragment of second protein which are similar in size to the fragment of the first protein . The optimized alignments are evaluated by a filter, which removes short fragments and checks for side chain orientations. Finally, they are classified by a clustering procedure. Besides the number of equivalent residues, additional optimization criteria were r.m.s.d., the number of distinct solutions and computation time requirements. The average number of equivalent residues and average r.m.s.d. are calculated from the top ranking alternative alignment of each structure pair rather than using all alternatives. The multiple solutions are sorted by the number of equivalent residues as the primary key and r.m.s.d. as the secondary key. The alignments with the highest number of equivalent residues and the lowest r.m.s.d. are then refined by a dynamic programming algorithm a score matrix  $S$  for every residues pair  $A_i, B_j$  is calculated by measuring the distance  $d_{A_i, B_j}$ . See p.745-746 and Fig 6 which illustrates



two fragments of 1bd9-A and 1rlw proteins which are aligned by ProSup.

***Double Patenting***

8. Claims 13-15, 24-26 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of co-pending applications 09/909809 or 09/910054.

Applicant submitted that double-patenting rejections will be addressed after identifying allowable subject matter.

***Conclusion***

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Michael Borin, Ph.D.  
Primary Examiner  
Art Unit 1631

mlb